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REPLY UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1626

PATENT
3273-0153P

NOV 0 5 2004

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Yasutaka ISHII et al.	Conf.:	1456
Appl. No.:	10/092,554	Group:	1626
Filed:	March 8, 2002	Examiner:	SHIAO

For: CATALYST COMPRISING A CYCLIC IMIDE COMPOUND AND PROCESS FOR PRODUCING ORGAINIC COMPOUNDS USING THE CATALYST

LARGE ENTITY TRANSMITTAL FORM
FOR REPLY AFTER FINAL UNDER 37 C.F.R. § 1.116

MS AF
Commissioner for Patents   November 5, 2004
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐   The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. § 1.8.

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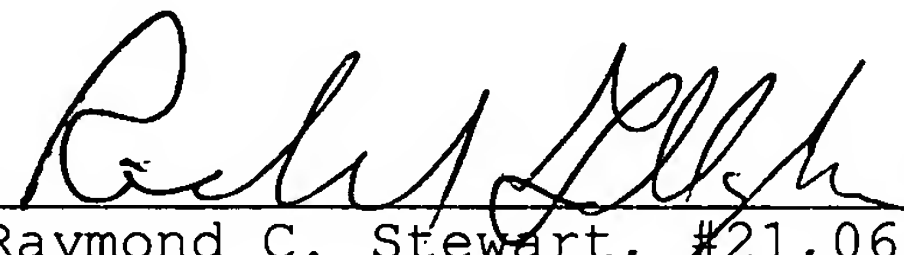
The fee has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA	RATE	ADDITIONAL FEE
TOTAL	11	−	20	=	0	$ 18	$0.00
INDEPENDENT	2	−	3	=	0	$ 88	$0.00
☐ FIRST PRESENTATION OF A MULTIPLE DEPENDENT CLAIM						$300	$0.00
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☐   Petition for   ( ) month(s) extension of time pursuant to 37 C.F.R. §§ 1.17 and 1.136(a). $0.00 for the extension of time.

☒   No fee is required.

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☐   Please charge Deposit Account No. 02-2448 in the amount of $0.00. This form is submitted in triplicate.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____ #28,781
     Raymond C. Stewart, #21,066

P.O. Box 747
Falls Church, VA 22040-0747
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RCS/RG/jmb
3273-0153P

Attachment(s)

MS AF
REPLY UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1626
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Appl. No.:   10/092,554   Group: 1626

Filed: March 8, 2002   Examiner: SHIAO

For: CATALYST COMPRISING A CYCLIC IMIDE
              COMPOUND AND PROCESS FOR PRODUCING
              ORGANIC COMPOUNDS USING THE CATALYST

REQUEST FOR RECONSIDERATION

Commissioner for Patents   November 5, 2004
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Office Action of August 10, 2004. Claims 1-4 and 10-14 are pending in the application.

Objection was raised to claims 1 and 2. The Examiner indicated that the claims both used the designation "Formula (I)" but that that designation referred to two different chemical structures. Actually, claim 1 refers to a Formula (I) - that is, Roman numeral "I", while claim 2 refers to a Formula (1) - that is, Arabic numeral "1". Thus there is no

inconsistency between the designations of the formulas in claims 1 and 2.

It is noted that the two lines on the lefthand side of Formula (I) are not used by Applicants to designate methyl groups. Instead they are bonds (open valences). Formula (1) in claim 2 describes preferred groups that can satisfy the open valences of Formula (I) in claim 1. This was previously recognized by the PTO, when the Examiner held that "claim 2 … is subgeneric to claim 1 … [and therefore] … claims 1-4 should be grouped together as a search for the imide skeleton". Office Action of 08/27/2003, page 2, bottom.

Accordingly, withdrawal of the objection to claims 1 and 2 is respectfully solicited.

Objection was raised to claims 3, 10, 13, and 14. Applicants respectfully point out that the substituent designation $\{R^xO-C(=O)\}_n-$ means that the benz ring in Formula (II) may carry 1, 2, 3, or 4 substituent groups each having the formula $R^xO-C(=O)-$. When the benz ring carries 2, 3, or 4 of those substituent groups, the 2, 3, or 4 groups can be the same or different. Therefore, withdrawal of the objection to claims 3, 10, 13 and 14 is respectfully solicited.

Claims 3 and 4 were rejected on the ground of obviousness-type double patenting over claims 4 and 7-9 of US 6,232,258 B1.

No Common Ownership. Double patenting rejections are appropriate only for "commonly **owned**" applications and patents. MPEP 706.02(l)(1). However, common **ownership** does not exist in the present situation, because US 6,232,258 B1 is owned by the entity 'Daicel Chemical Industries, Ltd. along with Yasutaka Ishii', while the present application is owned by the different entity 'Daicel Chemical Industries, Ltd alone'.

No Conflict In Subject Matter. The claims in question require an SP of less than or equal to 26 $(MPa)^{1/2}$. This clearly distinguishes the compounds of the present claims from the compounds of US 6,232,258 B1.

In order to deepen the Examiner's understand of the differences between the two invention, Applicants present the following discussion: The imide compound acts as a radical mediator mainly in the presence of molecular oxygen. The imide compound catalyzes at the active site of the N-O radical. See e.g. Ishii et al., *J. Org. Chem.,* 61:4520-4526 (1996). The Ishii et al. article shows phthalimide N-oxyl (45) having an N-O radical (Scheme 1 and Figure 3) which is a member of the class of imide compounds recited in present claim 1. US 6,232,258 B1 is based on the discovery that an oxidation

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provides a high yield when conducted in the presence of a strong acid. Accordingly, the imide compound and the strong acid are indispensable to the invention of the '258 patent. In contrast, the present invention involves the discovery that N-substituted cyclic imide compounds at an early stage exhibit low solubility in reaction solvents, which adversely affects yields. That problem is addressed in the present invention by way of a solubility parameter. Accordingly, N-substituted cyclic imides having specific solubility parameters are indispensable to the present invention. Thus two completely separate inventions are involved.

Ergo, no double patenting. Each of these reasons alone provides sufficient basis for withdrawal of the double patenting rejection, which action is respectfully solicited.

Should there be any outstanding issues that need to be resolved in the present application, the Examiner is respectfully requested to contact Richard Gallagher (Reg. No. 28,781) at (703) 205-8008.
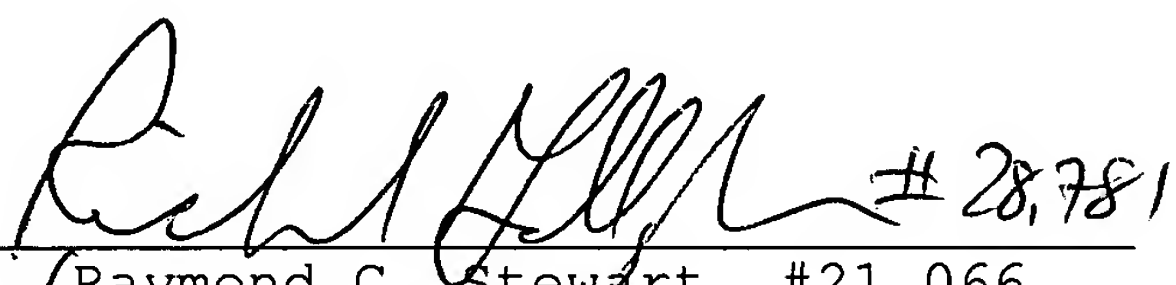
If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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3273-0153P

Enclosed:
Ishii et al., *J. Org. Chem.*, 61:4520-4526 (1996).

Alkane Oxidation with Molecular Oxygen Using a New Efficient Catalytic System: N-Hydroxyphthalimide (NHPI) Combined with Co(acac)n (n = 2 or 3)[†]

Yasutaka Ishii,* Takahiro Iwahama, Satoshi Sakaguchi, Kouichi Nakayama, and Yutaka Nishiyama

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564, Japan

A novel class of catalysts for alkane oxidation with molecular oxygen was examined. N-Hydroxyphthalimide (NHPI) combined with Co(acac)n (n = 2 or 3) was found to be an efficient catalytic system for the aerobic oxidation of cycloalkanes and alkylbenzenes under mild conditions. Cycloalkanes were successfully oxidized with molecular oxygen in the presence of a catalytic amount of NHPI and Co(acac)2 in acetic acid at 100 °C to give the corresponding cycloalkanones and dicarboxylic acids. Alkylbenzenes were also oxidized with dioxygen using this catalytic system. For example, toluene was converted into benzoic acid in excellent yield under these conditions. Ethyl- and butylbenzenes were selectively oxidized at their α-positions to form the corresponding ketones, acetophenone, and 1-phenyl-1-butanone, respectively, in good yields. A key intermediate in this oxidation is believed to be the phthalimide N-oxyl radical generated from NHPI and molecular oxygen using a Co(II) species. The isotope effect (k_H/k_D) in the oxidation of ethylbenzene and ethylbenzene-d_{10} with dioxygen using NHPI/Co(acac)2 was 3.8.

Introduction

Oxidative catalytic transformations of organic compounds with molecular oxygen (dioxygen) play a very important role in organic synthesis.[1] In particular, selective catalytic oxidation using dioxygen as the primary oxidant represents a critical technology and is an area of continued research and development. Several transition metal-catalyzed selective oxidations of alkanes involving the combined use of dioxygen and reducing agents such as H_2,[2] $NaBH_4$,[3] RCHO,[4] etc., have been reported. Recently, halogenated metalloporphyrins have been shown to be efficient catalysts for the direct reaction of alkanes with dioxygen without coreductants or stoichiometric oxidants to give alcohols and/or carbonyl compounds.[5] However, the development of an aerobic oxidation system in the absence of a reducing agent remains a very important and challenging subject in oxidation chemistry.

N-Hydroxyphthalimide (NHPI) was first used by Masui et al. as an efficient electron carrier in the electrochemical oxidation of secondary alcohols to ketones.[6] In the course of our study on the aerobic oxidation of benzylic compounds catalyzed by vanadomolybdophosphates,[7] we found that NHPI is a unique catalyst for the activation of molecular oxygen, as well as for the oxygenation of benzylic compounds such as fluorene[8] and the dehydrogenation of alcohols[9] with dioxygen under mild conditions. However, it is difficult to oxidize alkanes such as cyclohexane and toluene using NHPI alone.

We recently found that the catalytic activity of NHPI is markedly enhanced by the presence of a very small amount of Co(acac)n (n = 2 or 3) (0.05 equiv with respect to NHPI) as a cocatalyst. Thus, cycloalkanes and alkylbenzenes can be efficiently oxidized to the corresponding carbonyl compounds in an oxygen atmosphere under moderate conditions. This report presents our findings on the catalysis of alkane oxidations with atmospheric oxygen using NHPI combined with Co(acac)n (n = 2 or 3).

Results

1. Oxidation of Cycloalkanes with Dioxygen Using NHPI Combined with Transition Metals. The oxidation of cyclohexane (1) to a cyclohexanone (2)['](#)

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

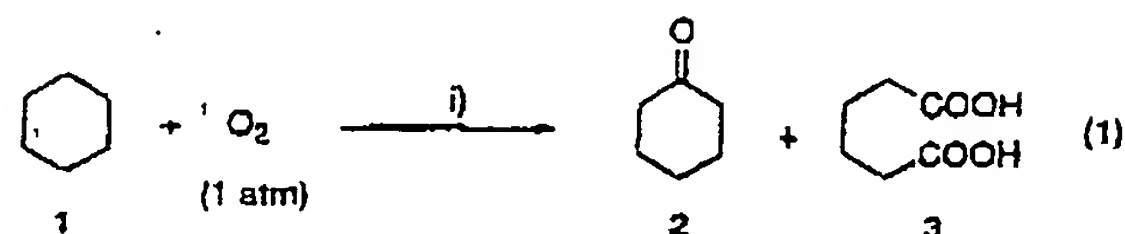@ Abstract published in Advance ACS Abstracts, June 1, 1996.

(1) (a) Sheldon, R. A.; Kochi, J. K. Metal-Catalyzed Oxidations of Organic Compounds; Academic Press: New York, 1981. (b) Hill, C. L. Activation and Functionalization of Alkanes; Academic Press: New York, 1989. (c) Simandi, L. Catalytic Activation of Dioxygen by Metal Complexes; Kluwer Academic Publisher: Boston, 1992. (d) The Activation of Dioxygen and Homogeneous Catalytic Oxidation; Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds.; Plenum Press: New York, 1993. (e) Mennier, B. Chem. Rev. 1992, 92, 1411. (f) Busch, D. H.; Alcock, N. W. Ibid. 1994, 94, 585.

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(3) Tabushi, I.; Yazaki, A. J. Am. Chem. Soc. 1979, 101, 6456.

(4) (a) Kaneda, K.; Haruna, S.; Imanaka, T.; Kawamoto, K. J. Chem. Soc., Chem. Commun. 1990, 1467. (b) Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. Chem. Lett. 1991, 1. (c) Murahashi, S.-I.; Oda, Y.; Naota, T. J. Am. Chem. Soc. 1992, 114, 7913. (d) Mukaiyama, T.; Yamada, T. Bull. Chem. Soc. Jpn. 1995, 68, 17. (e) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. J. Org. Chem. 1993, 58, 6421.

(5) (a) Lyons, J. E.; Ellis, P. E., Jr. Metalloporphyrins in Catalytic Oxidations; Sheldon, R. A., Ed.; Dekker: New York, 1994; p 291, and references cited therein. (b) Ellis, P. E., Jr.; Lyons, J. E. J. Chem. Soc., Chem. Commun. 1989, 1188. (c) Ellis, P. E., Jr.; Lyons, J. E. J. Chem. Soc., Chem. Commun. 1989, 1190. (d) Ellis, P. E., Jr.; Lyons, J. E. J. Chem. Soc., Chem. Commun. 1989, 1316. (e) Ellis, P. E., Jr.; Lyons, J. E. Catal. Lett. 1989, 3, 389. (f) Lyons, J. E.; Ellis, P. E., Jr. Catal. Lett. 1991, 8, 45. (g) Ellis, P. E., Jr.; Lyons, J. E. Coord. Chem. Rev. 1990, 105, 181. (h) Lyons, J. E.; Ellis, P. E., Jr.; Duranto, V. A. Studies in Surface Science and Catalysis; Grasselli, R. Ed.; Elsevier: New York, 1991; Vol. 67, p 99. (i) Ellis, P. E., Jr.; Lyons, J. E. Prepr. Am. Chem. Soc., Div. Pet. Chem. 1990, 35, 174. (j) Lyons, J. E.; Ellis, P. E., Jr.; Wagner, R. W.; Thompson, P. B.; Gray, H. B.; Hughes, M. E.; Hodge, J. A. Prepr. Am. Chem. Soc., Div. Pet. Chem. 1992, 37, 307.

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(7) (a) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. J. Org. Chem. 1992, 58, 6421. (b) Nakayama, K.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. Chem. Lett. 1993, 1699. (c) Fujibayashi, S.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. Chem. Lett. 1994, 1345.

(8) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. J. Org. Chem. 1995, 60, 3934.

(9) Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. Tetrahedron Lett. 1995, in press.

Alkane Oxidation with Molecular Oxygen

i) NHPI (10 mol%), Co(acac)₂ (0.5 mol%), CH₃COOH, 100 °C, 6 h

Table 1. Oxidation of Cyclohexane (1) with Dioxygen Catalyzed by NHPI In the Presence of Metal Salts under Various Reaction Conditions[a]

run	NHPI (mol %)	transition metal	temp (°C)	conv (%)	yield, %[b] 2	yield, %[b] 3[c]
1	10	—	100	1	trace	0
2	—	Co(acac)₂	100	trace	trace	0
3	10	Co(acac)₂	100	45	32	38
4	10	Co(acac)₃	100	42	35	40
5	5	Co(acac)₂	100	28	41	37
6	10	Co(acac)₂	75	30	48	30
7	10	Co(acac)₃	75	22	52	37
8[d]	10	Co(acac)₂	75	13	78	13
9[e]	10	Co(acac)₂	100	48	37	39
10[f]	10	Co(acac)₂	100	38	38	48
11	10	Co(OAc)₂·4H₂O	100	43	31	44
12	10	Mn(acac)₃	100	44	3	77
13	10	Cu(OAc)₂·H₂O	100	21	43	29
14	10	Fe(acac)₃	100	5	90	trace
15	10	Ni(acac)₂	100	0	—	—

[a] 1 (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI and transition metal (0.5 mol%) in acetic acid (12.5 mL) for 6 h. [b] Based on 1 reacted. [c] Yield of dimethyl adipate after esterification with excess methanol. [d] Acetonitrile was used as solvent. [e] Co(acac)₂ (1 mol%) was used. [f] Co(acac)₂ (0.25 mol%) was used.

cyclohexanol (4) mixture (ketone/alcohol (K/A) oil) is the first step in the two-step process for the production of adipic acid (3). Although there are several variants of this oxidation, the principal method is the autoxidation of cyclohexane in the presence of a metal catalyst such as Co or Mn salt.[10,11] An alternative cyclohexane oxidation uses a higher concentration of Co(III) acetate under oxygen pressure (20–30 atm).[12] However, the homogeneous catalytic oxidations of 1 using these methods have several problems, e.g., oxidative attack on the C—H bonds is slow and requires vigorous reaction conditions. To overcome these limitations, a new catalyst for selective oxidation with dioxygen must be identified. Hence, the catalytic oxidation of 1 with atmospheric oxygen under mild conditions is a challenge in industrial catalysis.

The oxidation of 1 with dioxygen (1 atm) using a new catalyst, NHPI, under selected conditions is shown in Table 1. Although a benzylic compound such as fluorene was efficiently oxidized to fluorenone in high yield (80%) with molecular oxygen (1 atm) in the presence of NHPI (10 mol %) in benzonitrile at 100 °C,[8] 1 was not oxidized by NHPI alone under these conditions. Thus, the effects of several transition metal salts on the NHPI-catalyzed oxidation of 1 in a dioxygen atmosphere were examined. An initial survey of representative transition metals demonstrated that a very small amounts of cobalt salts such as Co(acac)ₙ (n = 2 or 3) significantly facilitated the NHPI-catalyzed aerobic oxidation of 1 under moderate conditions. For example, the oxidation of 1 in the presence of NHPI (10 mol %) and Co(acac)₂ (0.5 mol %) in acetic acid at 100 °C for 6 h (standard conditions) gave cyclohexanone 2 (32%) and adipic acid 3 (38%) as the main products in the 45% conversion of 1 (run 3).[13] Oxidation did not take place in the absence of NHPI under these conditions (run 2). When Co(acac)₃ was used in place of Co(acac)₂ in this oxidation, 1 was converted to 2 and 3 at a slightly lower conversion (42%) (run 4). Similar effects of Co(acac)₂ and Co(acac)₃ on the oxidation of 1 were also observed at 75 °C (runs 6 and 7). Oxidation was considerably retarded by the use of acetonitrile as a solvent, while the selectivity of 1 to 2 at 75 °C was improved from 52% to 78% (run 8). Oxidation using Co(OAc)₂·4H₂O as a cocatalyst was similar to that with Co(acac)₂ (run 11). Mn(acac)₃, which is often used as a catalyst for autoxidation, was also effective in this oxidation. It is interesting to note that the addition of Mn(acac)₃ led to 3 rather than 2 in high selectivity (77%). This oxidation was slightly enhanced by adding Cu(OAc)₂·H₂O. In contrast to the effect of Co and Mn salts

in the NHPI-catalyzed oxidation of 1, Fe(acac)₃ had only a slight effect on the oxidation, and Ni(acac)₂ had no effect.

When the quantity of NHPI was halved (5 mol %), 1 was oxidized at a slightly lower conversion (28%) to form 2 and 3 in 41% and 37% selectivities, respectively. However, the effect of the concentration of Co(acac)₂ as the cocatalyst was clearly much less than that of NHPI. For the oxidation of 1 by NHPI (10 mol %) in the presence of Co(acac)₂ (1 mol %) (run 9), the results were almost the same as those with 0.5 mol % of Co(acac)₂ (run 3). It is noteworthy that the present aerobic oxidation of 1 resulted in 3 in higher selectivity, since the autoxidation of 1 in the presence of Co and Mn salts is known to lead to K/A oil (2 and 4) rather than 3 as the main product.[12] In particular, it is interesting that 1 was converted into 3 in one step in 77% selectivity by the NHPI/Mn(acac)₃ system under atmospheric oxygen at 100 °C.

On the basis of these results, several cycloalkanes were oxidized under standard conditions, i.e., in the presence of NHPI (10 mol %) and Co(acac)₂ (0.5 mol %) in an oxygen atmosphere (1 atm) using acetic acid at 100 °C for 6 h (Table 2).

For the oxidation of cyclopentane (5) under these conditions, the results were similar to those of 1 (run 1). However, cyclooctane (8) gave 1,4-cyclooctanedione (10) (16%) in addition to cyclooctanone (9) (50%) and suberic acid (11) (16%) in 93% conversion (run 2). Even when the amount of NHPI was reduced to 5 mol %, 8 was oxidized with a higher conversion (86%) (run 3). In contrast to 1, which was slightly oxidized by NHPI alone, 8 could be oxidized to 9 (63%), 10 (8%), and 11 (17%) in a 37% conversion by NHPI in the absence of any metals (run 4). The 1,4-diketone 10 is believed to be formed via intramolecular hydrogen abstraction by a transient peroxy radical generated from 8, as will be discussed later (Scheme 1). Indeed, the successive oxidation of 9 under these conditions led to dicarboxylic acid 11, while diketone 10 was not formed at all. Cyclododecane (12) was also converted into the corresponding ketone 13 and dicarboxylic acid 14 at a satisfactory conversion (66%) (run 5). During the oxidation of these cycloalkanes, alcohols such as cyclohexanol and cyclooctanol are be-
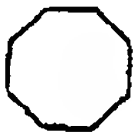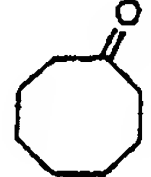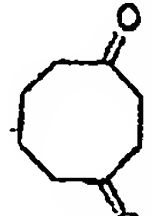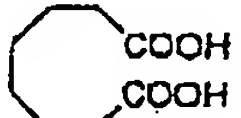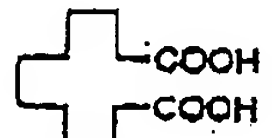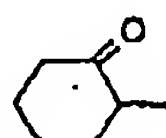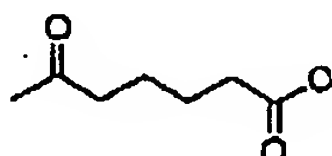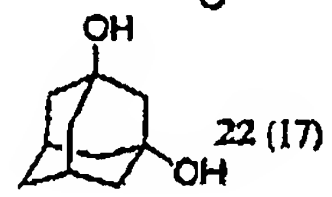
(10) Parshall, G. W.; Ittel, S. D. Homogeous Catalysis; 2nd ed.; John Wiley and Sons: New York, 1992; p 246, and reference cited therein.
(11) Simandi, L. Catalytic Activation of Dioxygen by Metal Complexes; Kluwer Academic Publisher: Boston, 1992; p 84, and reference therein.
(12) (a) Steeman, J. W. M.; Kaarsemaker, S.; Hoftyzer, P. J. Chem. Eng. Sci. 1961, 14, 139. (b) Miller, S. A. Chem. Process Eng. (London) 59, 50, 63. (c) Tanaka, K. Chem. Tech. 1974, 555, and references therein.
(13) By the GC-MS measurement of the reaction product of 1, the fomation of glutaric acid (up to 5%) and cyclohexyl acetate (up to 2%) other than 2 and 3 was confirmed.

Table 2. Oxidation of Cycloalkanes with Dioxygen Catalyzed by NHPI in the Presence of Co(acac)$_2$[a]

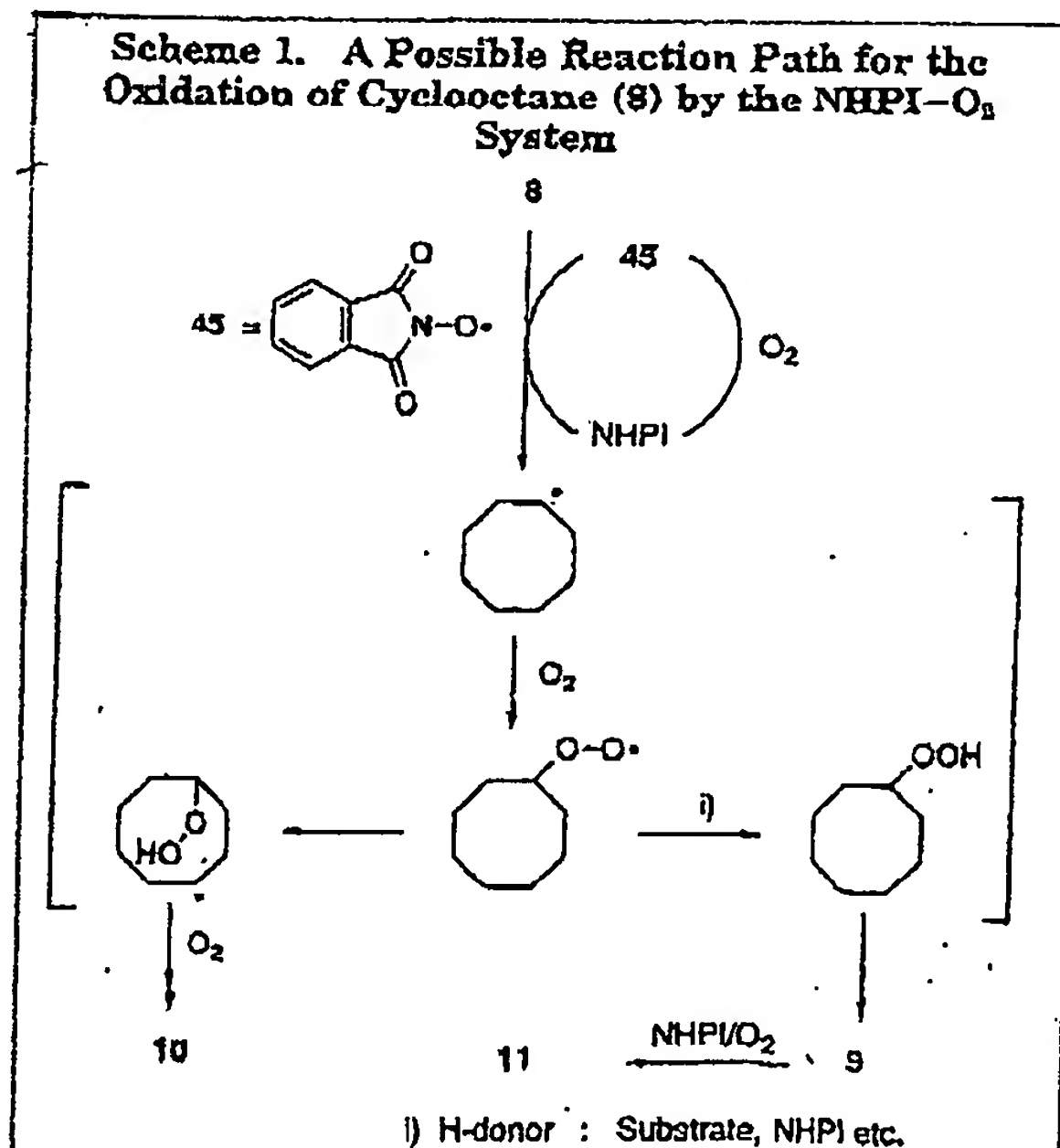| run	substrate		conv. (%)	products (%)[b,c]		
1		5	46	6 (27)	7 (32)	
2[d]		8	93	9 (50)	10 (16)	11 (16)
3[e]		8	86	9 (53)	10 (17)	11 (16)
4[f]		8	37	9 (63)	10 (8)	11 (17)
5		12	66	13 (34)	14 (30)	
6		15	77	16 (15)	17 (23)	18 (34)
7[g]		19	65	20 (71)	21 (9)	22 (17)
8		23	30	Octanols 24 (57)	Octanones 25 (14)	

[a] Substrate (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) and Co(acac)$_2$ (0.5 mol%) in acetic acid (12.5 mL) at 100 °C for 6 h. [b] Based on substrate reacted. [c] Yield of dicarboxylic acid was estimated as dimethyl ester after esterification with excess methanol. [d] Reaction time was 3 h. [e] NHPI (5 mol%) was used. [f] In the absence of Co(acac)$_2$. [g] Reaction was carried out at 75 °C for 3 h.

lieved to be formed, but very small amounts of the corresponding acetates were detected using GC-MS. It is believed that these alcohols are easily oxidized to ketones and/or dicarboxylic acids since they are more reactive than the starting cycloalkanes. In fact, cyclohexanol 4 was oxidized to 2 in 92% yield in acetonitrile at 75 °C.[9]

Methylcyclohexane (15) gave keto carboxylic acid 18 as a major product along with 2-methylcyclohexanone (16) and 1-methylcyclohexanol (17) (run 6). The independent oxidations of 16 and 17 under these reaction conditions were carried out to reveal the reaction path to 18. The oxidation of 16 gave 18, while 17 was a less reactive substrate. Thus, 18 was a further oxidation product of 16, but not of 17. The oxidation of adamantane (19) at 75 °C for 3 h gave 1-adamantanol (20) (71%), in which the tertiary C—H bond was selectively oxygenated, together with small amounts of 2-adamantanone (21) (9%) and 1,3-adamantanediol (22) (17%) in 65% conversion (run 7). The product ratio of the tertiary C—H bond to the secondary one was approximately 7.8. The aerobic oxidation of 19 using the PW$_9$Fe$_2$Ni heteropolyanion reportedly gives 20 (76%), 21 (12%), and 2-adamantanol (12%) in 29% conversion.[14] On the other hand, the oxidation of n-alkane such as n-octane (23) by this system gave a mixture of 2-, 3-, and 4-octanols 24 and the corresponding octanones 25 (run 8).

2. Oxidation of Alkylbenzenes Using NHPI Combined with Co(acac)$_2$. Various alkylbenzenes are known

(14) Mizuno, N.; Tateishi, M.; Hirose, T.; Iwamoto, M. Chem. Lett. 1993, 2137.

Scheme 1. A Possible Reaction Path for the Oxidation of Cyclooctane (8) by the NHPI–O$_2$ System

i) H-donor : Substrate, NHPI etc.

to be oxidized with dioxygen in the presence or absence of transition metals.[15]

The oxidation of several alkylbenzenes with dioxygen was attempted using the NHPI/Co(acac)$_2$ system (Table 3, runs 1–11). The oxidation of toluene (26) with NHPI

Alkane Oxidation with Molecular Oxygen

Table 3. Oxidation of Alkylbenzenes with Dioxygen Catalyzed by NHPI in the Presence of Co(acac)$_2$^{a}

run	substrate	conv (%)	products (%)^b
1	toluene (26)	92	benzoic acid (27) (99)
2^c	26	9	27 (trace)
3	p-tert-butyltoluene (28)	97	p-tert-butylbenzoic acid (29) (95)
4	p-methoxytoluene (30)	98	p-methoxybenzoic acid (31) (85)
5	ethylbenzene (32)	91	acetophenone (33) (93)
6	n-butylbenzene (34)	90	1-phenyl-1-butanone (35) (67)
7	p-xylene (36)	94	p-toluic acid (37) (78), terephthalic acid (38) (15)
8^{d,e}	36	89	37 (23), 38 (68)
9	o-xylene (39)	92	o-toluic acid (40) (80), phthalic acid (41) (14)^f
10^{d,e}	39	99	40 (71), 41 (23)
11	cumene (42)	31	33 (54), 2-phenyl-2-propanol (43) (10), phenol (44) (17)

^{a} Substrate (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in acetic acid (12.5 mL) at 100 °C for 6 h. ^{b} Based on substrate reacted. ^{c} In the absence of Co(acac)$_2$. ^{d} NHPI (20 mol %) was used. ^{e} Reaction was carried out at 100 °C for 12 h. ^{f} Yield of dicarboxylic acid was estimated as dimethyl ester after esterification with excess methanol.

(10 mol %) in the presence of Co(acac)$_2$ (0.5 mol %) in acetic acid in an oxygen atmosphere at 100 °C for 6 h exclusively gave benzoic acid (27) (>99%) at 92% conversion (run 1). The same oxidation with 26 by NHPI alone produced only a trace amount of 27 (run 2). Toluene (26) has been reported to be oxidized with air in the presence of cobalt(II) 2-ethylhexanoate at 140–190 °C and up to 10 atm of pressure to give 27 in about a 80% yield at 40–65% conversion.[15a] Consequently, the NHPI/Co-(acac)$_2$ system is thought to be a useful catalytic system for the aerobic oxidation of 26. Similarly, p-tert-butyltoluene (28) and p-methoxytoluene (30) were oxidized to p-tert-butylbenzoic acid (29) and p-methoxybenzoic acid (31), respectively, in good yields (runs 3 and 4). In the oxidation of ethylbenzene (32), acetophenone (33) was obtained in good yield (run 5). n-Butylbenzene (34) was likewise oxidized to give 1-phenyl-1-butanone (35) in slightly lower selectivity (67%). To evaluate the potential for the oxidation of the disubstituted alkylbenzenes, the oxidation of xylene was examined. p-Xylene (36) was converted into the corresponding mono- and dicarboxylic acids 37 and 38, the ratio of which depended on the reaction time. The oxidation of 36 under the standard conditions gave p-toluic acid (37) in a 78% selectivity with 94% conversion. When the reaction time was prolonged to 12 h, terephthalic acid (38) was obtained in 68% yield. However, it was difficult to convert o-xylene (39) to phthalic acid (41) in high selectivity (runs 9 and 10). Cumene (42) is known to be oxidized by dioxygen to give cumene hydroperoxide, which is converted to phenol and acetone.[16] However, 42 was oxidized with difficulty by the NHPI/Co(acac)$_2$ system to form acetophenone (33) (54%), 2-phenyl-2-propanol (43) (10%), and phenol (44) (17%) in 31% conversion. The low conversion of 42 was due to the formation of phenol 44. The oxidation of 42 by this system in the presence of 44 (10 mol %) was markedly inhibited, and only trace amounts of 33 and 43 were formed.

To gain additional insight into NHPI/Co(acac)$_2$-catalyzed aerobic oxidation, the absorption rate of dioxygen during the oxidation of 32 with several catalytic systems was measured using a constant-pressure absorption apparatus. Figure 1 shows the time-dependence curves the O$_2$ uptake of 32 under atmospheric pressure (1 atm) at 80 °C. It is interesting to compare the rate of O$_2$ uptake by 32 in the NHPI/Co(acac)$_2$ and NHPI/Co(acac)$_3$
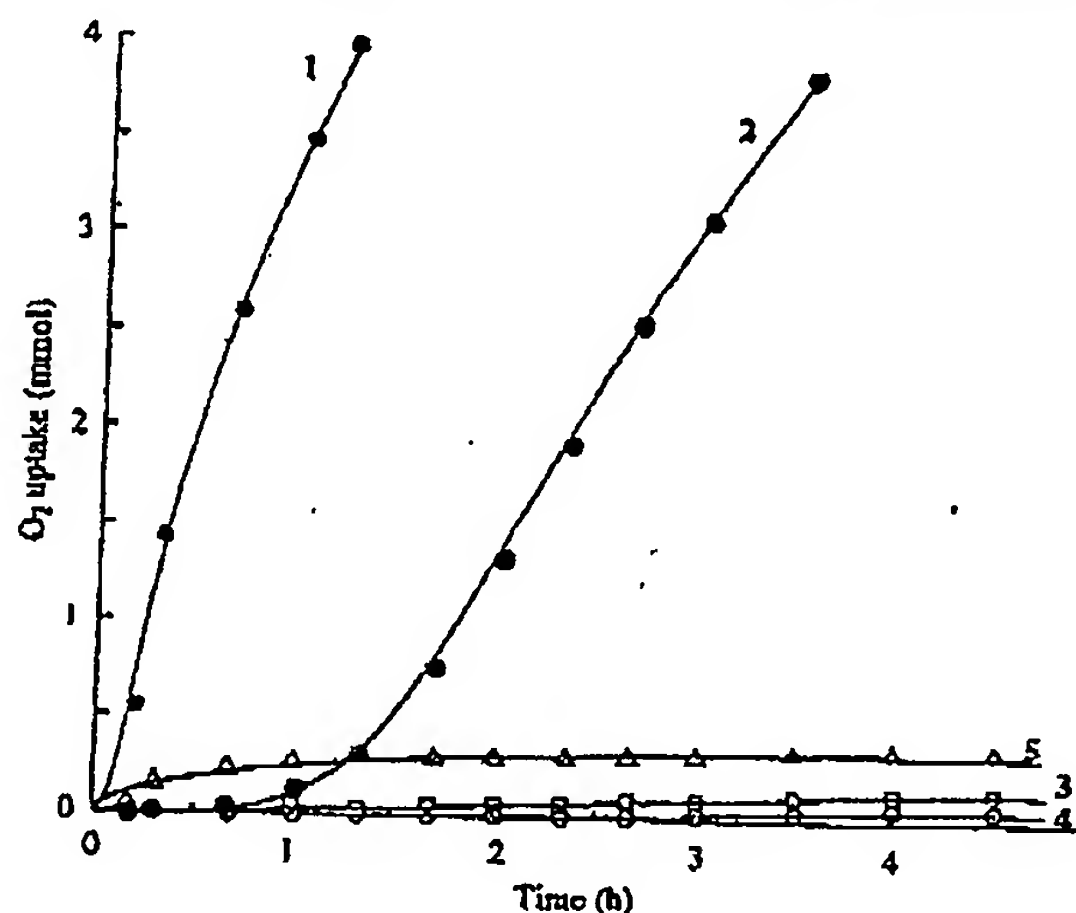

Figure 1. Time dependence curves of O$_2$ uptakes for the oxidation of ethylbenzene (32) under atmospheric pressure of dioxygen by various catalysts. Conditions: Ethylbenzene (32) (10 mmol) was allowed to react with dioxygen (1 atm) in acetic acid (25 mL) at 80 °C. (1) NHPI (10 mol %), Co(acac)$_2$ (0.5 mol %); (2) NHPI (10 mol %), Co(acac)$_3$ (0.5 mol %); (3) NHPI (10 mol %); (4) Co(acac)$_2$ (0.5 mol %); (5) AIBN (5 mol %), Co(acac)$_2$ (0.5 mol %).

systems. No induction period was observed in O$_2$ uptake by 32 with NHPI/Co(acac)$_2$, while that with the NHPI/Co(acac)$_3$ system did not occur until after about 1.5 h. Almost no O$_2$ uptake was observed in the oxidation of 32 by NHPI, Co(acac)$_2$, or Co(acac)$_3$ alone. In the same oxidation using the AIBN/Co(acac)$_2$ system, the results were almost the same except for O$_2$ uptake in the early stage of the reaction by radicals generated from AIBN. The isotope effect during the present oxidation was estimated by measuring the oxygen uptake by ethylbenzene (32) and ethylbenzene-d_{10} (32-d_{10}) (Figure 2). The observed isotope effect, k_H/k_D, was approximately 3.74. In addition, the oxidation of 32 in the presence of hydroquinone (1 mol %) under the standard conditions did not occur at all. These results strongly suggest that the present aerobic oxidation proceeds via a reaction pathway similar to that in free radical autooxidation.

Discussion

Masui *et al.* suggested that phthalimide N-oxyl (45) is a key species in the electrochemical oxidation of alcohols

(15) (a) Parshall, G. W.; Ittel, S. D. *Homogeous Catalysis*, 2nd ed.; n Wiley and Sons: New York, 1992; p 256. (b) Sheldon, R. A.; Kochi, 《. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic ss: New York, 1981; p 315.

(16) Reichle, W. T.; Konrad, F. M.; Brooks, J. R. *Benzene and its ustrial Derivatives*; Hancock, E. G., Ed.; Benn: London, 1975.
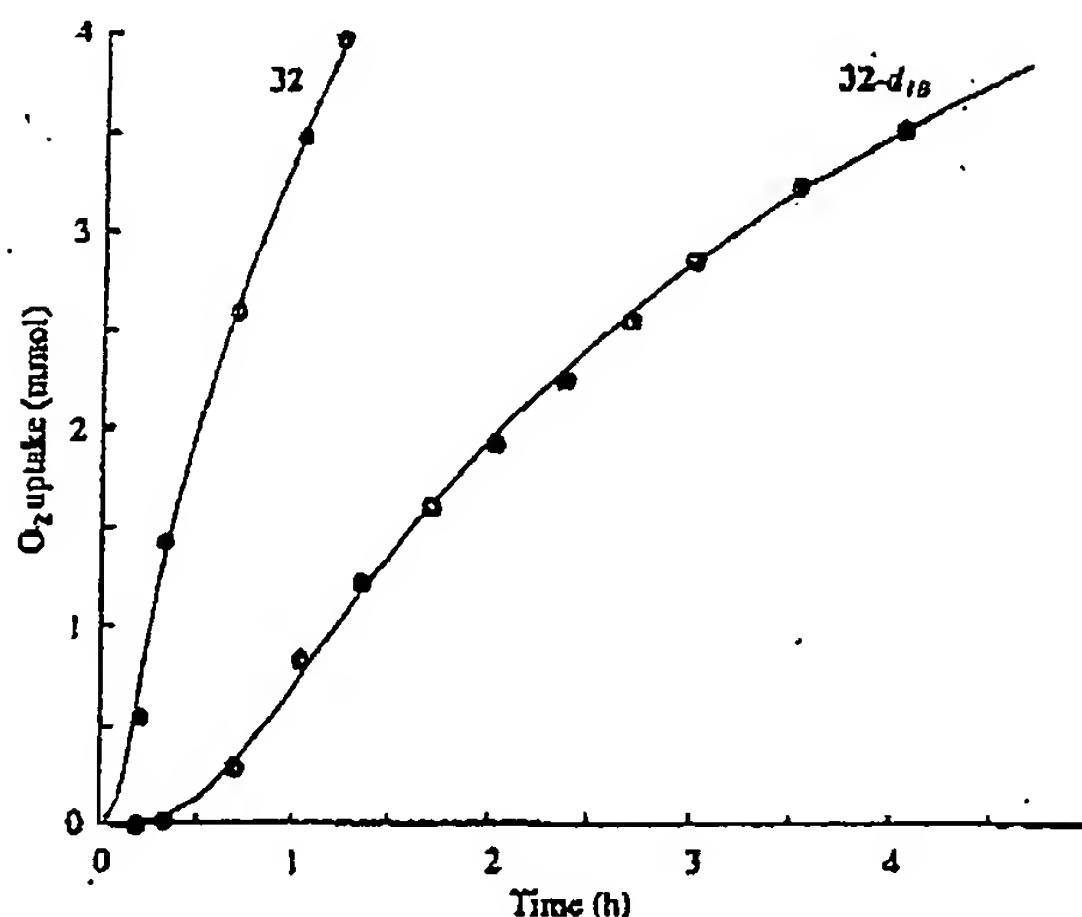
Figure 2. Time dependence curves of O_2 uptakes for the oxidation of ethylbenzene (32) and ethylbenzene-d_{10} (32-d_{10}) by NHPI/Co(acac)$_2$-O_2 system. Conditions: Ethylbenzene (32) (10 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in acetic acid (25 mL) at 80 °C.
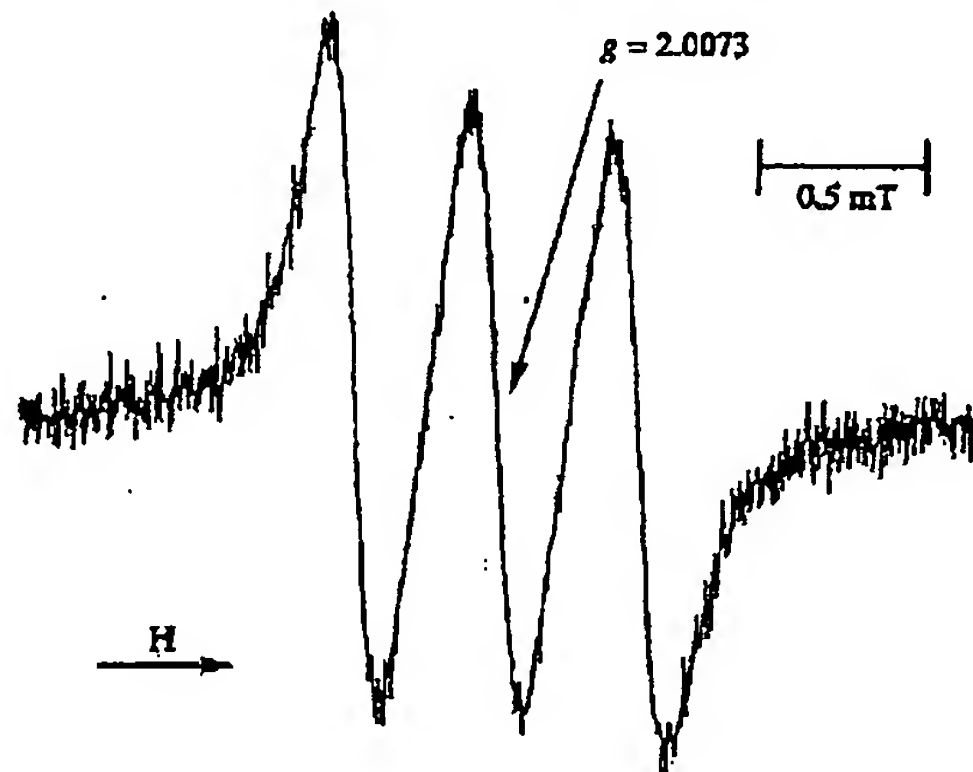

Figure 3. ESR spectrum of N-oxyl radical 45 under dioxygen in benzonitrile at 80 °C.

to ketones using NHPI as an electron carrier.[17] To confirm the formation of phthalimide N-oxyl (45) in the present NHPI-catalyzed aerobic oxidation, electron spin resonance (ESR) measurements were carried out under selected conditions. When a benzonitrile solution of NHPI was exposed to dioxygen at 80 °C for 1 h,[18] the ESR spectrum attributed to 45 was clearly observed as a triplet signal based on hyperfine splitting (hfs) by the nitrogen atom ($g = 2.0074$, $a_N = 0.43$ mT) (Figure 3). The g-value and hfs constant observed for 45 were consistent with those ($g = 2.0073$, $a_N = 0.423$ mT) reported by Mackor et al.[19] No ESR signal was observed under argon. It is noteworthy that 45 is easily formed by exposing NHPI to molecular oxygen under moderate conditions.

(17) (a) Masui, M.; Hosomi, K.; Tsuchida, K.; Ozaki, S. Chem. Pharm. Bull. 1985, 33, 4798. (b) Ueda, O.; Nayama, M.; Ohmori, H.; Masui, M. Chem. Pharm. Bull. 1987, 35, 1372.

(18) ESR spectra were obtained under the following conditions: sweep width 327 ± 2.5 mT; modulation 0.1 mT; and microwave power 1 mW. Benzonitrile containing 10^{-2} mmol of NHPI was exposed under oxygen atmosphere at 80 °C for 1 h. The air in the ESR tube was replaced by dioxygen gas by means of the freeze-pump-thaw method. The ESR parameter was determined by using solid Mn^{2+} ($g = 2.034$) as a standard.

Furthermore, 2-norbornene (46) was allowed to react with NHPI under an oxygen atmosphere in acetonitrile at 60 °C. The reaction gave N-(2-hydroperoxybicyclo[2.2.1]heptan-2-yloxy)phthalimide (47) in 52% yield (eq 2). Treatment of triphenylphosphine with 47 produced triphenylphosphine oxide (94%) and N-(hydroxybicyclo[2,2,1]heptan-2-yloxy)phthalimide (48) (83%) (eq 3). This
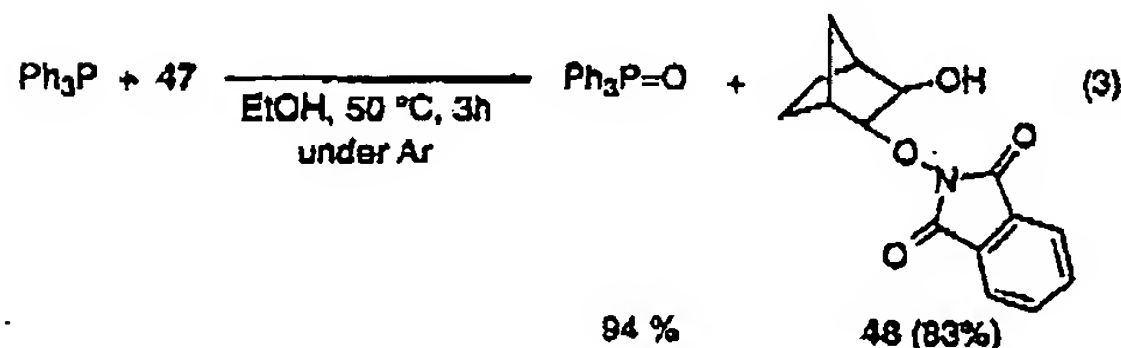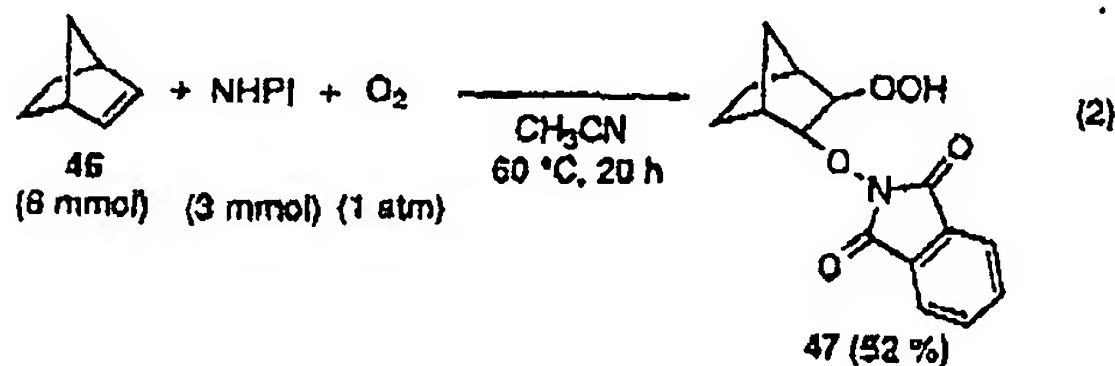
result definitely shows that the radical species 45 is smoothly generated from NHPI and molecular oxygen in the absence of transition metals under mild conditions. Hence, the oxidation process of alkanes such as cyclooctane 8, which is oxidized by dioxygen using NHPI alone, can be outlined as in Scheme 1. The first step of the reaction is thought to involve the generation of the phthalimide N-oxyl radical 45 from NHPI and dioxygen. The resulting 45 abstracts a hydrogen atom from the substrates to form alkyl radicals, subsequent oxygenation of which by dioxygen produces peroxy radicals, which are converted to ketones and/or dicarboxylic acids. In some cases, intramolecular hydrogen abstraction by the resulting alkyl peroxy radical occurs, and leads to the formation of the diketone 10.

Unfortunately, we are currently unable to clearly explain the role of Co(acac)$_n$ as a cocatalyst in NHPI-catalyzed aerobic oxidation. However, we can make several proposals which seem to agree with the experimental results.

As mentioned earlier, no induction period was observed in the oxidation of ethylbenzene 32 with the NHPI/Co(acac)$_2$ system. However, oxygen uptake by 32 did not occur until after about 1.5 h with the NHPI/Co(acac)$_3$ system. This finding is in accord with the results of adding NHPI alone to Co(acac)$_2$ or Co(acac)$_3$. When NHPI was added to an acetic acid solution of Co(acac)$_2$, the color of the solution immediately changed from pink to violet, and a mixture of several complexes 49 was obtained. On the other hand, the same procedure with Co(acac)$_3$ led to no color change of the solution, and most of the starting materials were recovered unchanged. However, when ethylbenzene 32 was added to this solution, the color of the solution gradually changed to violet and finally became the same as that in the NHPI/Co(acac)$_2$ system to form complexes similar to those derived from NHPI and Co(acac)$_2$. This result indicates that Co(acac)$_3$ is gradually reduced to Co(II) with 32 via

(19) Mackor, A.; Wajer, Th. A. J. W.; de Boer, Th. J. Tetrahedron 1968, 24, 1623.

a well-known one-electron transfer process,[20] and the resulting Co(II) species readily reacts with NHPI to produce complexes similar to those derived from the NHPI/Co(acac)$_2$ system. These results well reflect the differences in the induction period between the NHPI/Co(acac)$_2$ and NHPI/Co(acac)$_3$ systems during O$_2$ uptake by 32. The induction period of 1.5 h observed with the NHPI/Co(acac)$_3$ system may represent the time required to reach a threshold concentration of Co(II) by one-electron transfer from 32 to Co(III).

On the other hand, 32 and 1 were oxidized using the complexes 49 obtained from NHPI and Co(acac)$_2$ (eq 4). 32 was oxidized to acetophenone 33 in 69% yield, while 1 failed to be oxidized by these complexes.
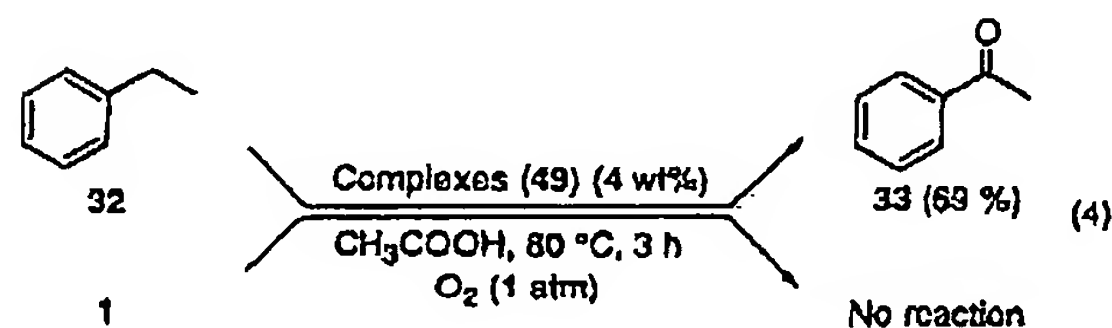
Although the role of the Co(II) species in the NHPI-catalyzed aerobic oxidation is not fully understood, the Co(II) species may be related to the generation of the phthalimide *N*-oxyl radical 45 from NHPI. However, it appears that the present results do not detract from the importance of the discovery of a new mode of dioxygen activation by the NHPI/Co(acac)$_n$ (n = 2 or 3) system.

Experimental Section

^{1}H and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, with tetramethylsilane as an internal standard. Infrared (IR) spectra were measured using NaCl or KBr pellets. A GC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1). Oxygen-absorption rates were measured with an isobaric gas-absorption apparatus under a closed-flow system (2 ± 0.1 L oxygen/h) equipped with an electrolyzer. ESR measurements were performed on a JEOL-FE-1X (X-band) with 100-kHz field modulation.

All starting materials and catalysts were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

General Procedure for Oxidation of Cycloalkanes. An acetic acid (12.5 mL) solution of cycloalkane (5 mmol), NHPI (82 mg, 10 mol %), and Co(acac)$_2$ (7.5 mg, 0.5 mol %) was placed in a three-necked flask equipped with a balloon filled with O$_2$. The mixture was stirred at 100 °C for 6 h. After removing the solvent under reduced pressure, methanol (25 mL) and a catalytic amount of concd H$_2$SO$_4$ were added to the resulting mixture and stirred at 65 °C for 15 h. The resulting solution was extracted with diethyl ether (20 mL × 3). The combined extracts were dried over anhydrous MgSO$_4$. Removal of solvent under reduced pressure gave a clean liquid, which was purified by column chromatography on silica gel, *n*-hexane/AcOEt = 5/1) to give the corresponding oxygenated products.

Ketones 2, 6, 9, 13, 16, 21, and 24, alcohols 20 and 25, and dicarboxylic acids 3, 7, 11, and 14 were identified by comparing the isolated products with authentic samples.

1,4-Cyclooctanedione (10): ^{1}H NMR (CDCl$_3$) δ 1.83–1.87 (m, 4H), 2.40–2.44 (m, 4H), 2.71 (s, 4H); ^{13}C NMR (CDCl$_3$) δ

24.4, 40.6, 41.3, 213.7; IR (NaCl) 2941, 2865, 1697, 1445, 1334, 1108, 1091, 946, 822 cm^{-1}.

1-Methylcyclohexanol (17): ^{1}H NMR (CDCl$_3$) δ 1.21 (s, 3H), 1.36 (s, 1H), 1.44–1.63 (m, 10H); ^{13}C NMR (CDCl$_3$) δ 22.6, 25.6, 29.5, 39.4, 69.9; IR (NaCl) 3352, 2930, 2859, 1170, 1120, 967, 911 cm^{-1}.

6-Oxoheptanoic acid (18): ^{1}H NMR (CDCl$_3$) δ 1.62–1.65 (m, 4H), 2.16 (s, 3H), 2.36–2.40 (m, 2H), 2.45–2.48 (m, 2H), 11.02 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 23.0, 24.0, 29.9, 33.8, 43.2, 179.8, 209.0; IR (NaCl) 3046, 2945, 1712, 1414, 1369, 1235, 1176 cm^{-1}.

1,3-Adamantandiol (22): ^{1}H NMR (CDCl$_3$) δ 1.61–1.77 (m, 14H), 2.34 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 31.1, 34.5, 43.7, 52.5, 70.3; IR (KBr) 3349, 2931, 1333, 1030 cm^{-1}.

General Procedure for Oxidation of Alkylbenzenes. An acetic acid (12.5 mL) solution of alkylbenzenes (5 mmol), NHPI (82 mg, 10 mol %), and Co(acac)$_2$ (7.5 mg, 0.5 mol %) was placed in a three-necked flask equipped with a balloon filled with O$_2$. The mixture was stirred at 100 °C for 6 h. After removal of the solvent under reduced pressure, the products were purified by column chromatography on silica gel to give the corresponding oxygenated products.

Products 27, 29, 31, 33, 37, 38, 40, 41, and 44 were identified by comparing of the isolated products with authentic samples.

1-Phenyl-1-butanone (35): ^{1}H NMR (CDCl$_3$) δ 0.98–1.04 (t, J = 7.3 Hz, 3H), 1.71–1.85 (m, 2H), 2.92–2.98 (t, J = 7.6 Hz, 2H), 7.43–7.58 (m, 3H), 7.95–7.98 (d, J = 7.9 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 200.4, 137.1, 132.8, 128.5, 128.0, 40.5, 17.7, 13.9; IR (NaCl) 2963, 1688, 1449, 1214, 692 cm^{-1}.

2-Phenyl-2-propanol (43): ^{1}H NMR (CDCl$_3$) δ 1.55 (s, 6H), 2.40 (s, 1H), 7.19–7.50 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 31.6, 72.4, 124.4, 126.5, 128.1, 149.1; IR (NaCl) 3374, 2976, 2359, 1446, 1363, 764, 699, 544 cm^{-1}.

General Procedure for Measuring Oxygen-Absorption Rates. Oxygen-absorption rates were measured with an isobaric gas-absorption apparatus in a closed-flow system (2 ± 0.1 L oxygen/h) equipped with an electrolyzer using 25 mL of acetic acid containing ethylbenzene (1.06 g, 10 mmol), NHPI (163 mg, 10 mol %) and Co(acac)$_2$ (14.7 mg, 0.5 mol %) at 80 °C. Oxygen absorption was periodically measured in the constant-pressure closed system.

Reaction of 46 with NHPI. An acetonitrile (5 mL) solution of 2-norbornene (564 mg, 6 mmol) and NHPI (489 mg, 3 mmol) was placed in a three-necked flask equipped with a balloon filled with O$_2$. The mixture was stirred at 60 °C for 20 h. After the reaction, acetonitrile was removed under reduced pressure to give a white crystal, which was purified by diethyl ether (30 mL) to give the hydroperoxide 47 in 52% yield.

***N*-(2-Hydroperoxybicyclo[2.2.2]heptan-2-yloxy)phthalimide (47):** ^{1}H NMR (CDCl$_3$) δ 1.16–1.41 (m, 2H), 1.48–1.65 (m, 2H), 2.04 (d, J = 10.0 Hz, 1H), 2.31 (s, 1H), 2.94 (s, 1H), 4.14 (d, J = 5.3 Hz, 1H), 4.36 (d, J = 5.3 Hz, 1H), 7.79–8.55 (m, 4H), 10.65 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 22.9, 25.9, 33.6, 39.8, 41.7, 89.0, 93.6, 123.9, 128.6, 134.9, 164.3; IR (KBr) 3381, 2950, 1789, 1732, 1379, 1188, 993, 878, 699, 520 cm^{-1}. Anal. Calcd for C$_{15}$H$_{15}$NO$_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.17; H, 5.18; N, 4.82.

Reaction of 47 with Triphenylphosphine. An ethanol (30 mL) solution of 47 (289 mg, 1 mmol) and Ph$_3$P (262 mg, 1 mmol) was placed in a three-necked flask, and the mixture was stirred at 50 °C for 3 h under an Ar atmosphere. After the reaction, ethanol was removed under reduced pressure to give a white crystal, which was purified by diethyl ether (30 mL) to give triphenylphosphine oxide in 94% yield along with alcohol 48 (83%).

***N*-(2-Hydroxybicyclo[2.2.2]heptan-2-yloxy)phthalimide (48):** ^{1}H NMR (CDCl$_3$) δ 1.05–1.12 (m, 3H), 1.21 (d, J = 10.5 Hz, 1H), 1.46–1.63 (m, 4H), 2.05 (d, J = 10.5 Hz, 1H), 2.29 (s, 1H), 2.86 (s, 1H), 3.91 (s, 1H), 4.00 (s, 1H), 7.75–7.87 (m, 4H), 10.65 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 24.0, 24.9, 32.7, 41.3, 43.2, 75.8, 93.2, 123.7, 128.6, 134.7, 164.0; IR (KBr) 3451, 2964, 1783, 1730, 1379, 1186, 999, 878, 782, 703, 518 cm^{-1}.

(20) The oxidation of alkylbenzenes[21] and cyclohexane[22] by Co(III) on is known to involve one-electron transfer from substrates to Co(II), yielding Co(II) ion and radical cations.

(21) Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* 1969, 91, 6830.

(22) Onopchenko, A.; Schulz, J. G. D. *J. Org. Chem.* 1973, 38, 3729.

These values were consistent with those reported in the literature.[23]

Preparation of Complexes 49. A mixture of NHPI (294 mg, 2 mmol) and Co(acac)$_2$ (235 mg, 0.8 mmol) in acetic acid (15 mL) was stirred at 80 °C under an oxygen atmosphere. After 0.5 h, the reaction mixture was evaporated, and an orange solid was obtained. The resulting solid was washed using acetonitrile, and then the complexes 49 were obtained (271 mg).

Oxidation of 1 and 32 Catalyzed by Complexes 49. To a stirred solution of complex (49) (21 mg, 4 wt %) in acetic acid (10 mL) was added 1 or 32 (5 mmol), and the reaction mixture was fitted with a balloon filled with oxygen. The mixture was stirred at 80 °C for 3 h. The workup was performed using the same method as previously described.

Supporting Information Available: Copies of spectra of compounds 10, 17, 18, 22, 35, 43, 47, and 48 (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951970L

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